II. REMARKS

Reconsideration of the rejections set forth in the Office action dated May 8, 2002 is respectfully requested. Applicants have carefully considered the points raised in the Office action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case in condition for allowance.

Claims 1-57 were pending in the present application. By virtue of this response, claims 1 and 8 have been amended, and new claims 58-62 have been added. Accordingly, claims 1-62 are currently under consideration. The amendments are made solely to promote prosecution without prejudice or disclaimer of any of the previously or presently claimed subject matter.

Amendments

Claim 1 has been amended to bring out the feature that the claimed invention is directed to a method of treating and/or ameliorating symptoms of neuronal damage associated with a cerebral ischemic condition in a mammalian subject. Support for this aspect of the invention can be found, for example at page 17 (lines 7-12), page 18 (lines 16-23), page 41 (lines 20-26), and page 43 (lines 1-6).

Claim 8 has been amended to insert the proper name of the metabolite 2,7,8-trimethyl-2-(β-carboxy-ethyl)-6-hydroxy chroman, abbreviated as "gamma-CEHC." Support for this feature of the invention is found, for example, at page 14, lines 19-25. Applicants note that the Greek letter "γ" and its written out form (gamma) are used interchangeably throughout the specification.

Claim 10 has been amended to correct the spelling of the term "thromboembolus."

New claims 58-62 are added to bring out the feature that the method of the claimed invention is effective to reduce certain specific forms of neuronal damage, namely, total cerebral infarct volume, total cerebral ischemic damage, cerebral edema, and cognitive dysfunction. Support for these aspects of the invention can be found throughout the specification, for example at page 7, lines 13-19, page 11, lines 15-20, page 19, lines 1-18, and page 68, lines 13-16 (as further supported by the descriptions found at page 66, line 18 to page 67, line 34).

Accordingly, applicants respectfully submit that no new matter is added by way of the foregoing amendments and additions to the claims.

Rejection of Claims 1-57 Under 35 U.S.C. § 103(a)

A. Claims 1-57 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Wechter, W.J., U.S. Patent No. 6,048,891 ("Wechter"). It is the Examiner's position that Wechter's teaching of treating thromboembolic diseases would render obvious the applicants' claimed invention. The Examiner acknowledges that Wechter does not describe cerebral ischemic conditions, but asserts that that known anti-oxidant properties of tocopherols would make obvious such conditions, in view of Wechter. Applicants respectfully traverse these rejections, in view of the following remarks.

1. The Invention. The applicants' claimed invention is directed to a method of treating or ameliorating symptoms of neuronal damage associated with a cerebral ischemic condition in a mammalian subject. According to an important feature of the invention, an effective amount of a non-alpha tocopherol enriched tocopherol composition is administered to subjects resulting in a reduction of neuronal damage related to the cerebral ischemic condition. Exemplary symptoms of neuronal damage associated with cerebral ischemia include, for example, neuronal cell death, cerebral tissue edema, and cognitive dysfunction, and are further described throughout the specification, for example, at page 7, lines 13-19.

2. The Cited Prior Art. Wechter describes the use of various tocopherols and metabolites to treat, among other maladies, thromboembolic disease. Thromboembolic disease is generally characterized as the obstruction of a blood vessel with thrombotic material (such as a blood clot) carried by the blood from the site of origin. Wechter exemplifies this use by way of an example (Example 23, mentioned by the Examiner), in which platelet aggregation is reduced after administration of a combination of gamma tocopherol and LLU-alpha. Applicants respectfully submit that while platelet aggregation is one of the sequelae of events that lead up to formation of a thrombus or a thromboembolus, neither platelet aggregation or thrombus or

thromboembolus formation is a symptom of neuronal damage resulting from or related to cerebral ischemia.

Nowhere does Wechter describe or suggest the use of non-alpha tocopherols (or their metabolites) in a method of reducing a symptom of neuronal damage associated with a cerebral ischemic condition, nor does Wechter show or suggest that non-alpha tocopherols or their metabolites are effective to reduce neuronal damage associated with cerebral ischemia. Nor does the "general knowledge" cited by the Examiner make up for the deficiencies in Wechter.

3. Analysis. The Examiner has asserted that the claimed invention is obvious over Wechter, in view of what the Examiner states as general knowledge of persons skilled in the art of neurology - that "...non-alpha tocopherols, in particular gamma tocopherol, exhibit antioxidant efficacy in inhibiting low density lipoprotein oxidation, platelet aggregation and arterial thrombogenesis." (p. 3, Office Action mailed May 8, 2002) In short, the Examiner is asserting that the invention is prima facie obvious over Wechter in view of what she asserts to be general knowledge available to one of ordinary skill in the art.

In order to support a claim of *prima facie* obviousness, it is incumbent upon the Examiner to show (i) that there is a motivation or suggestion in the references or in the knowledge generally available to persons of ordinary skill in the art, to modify the references or combine the teachings, (ii) that there is a reasonable expectation of success, and (iii) that the reference or references teach or suggest all the claim limitations. MPEP 2142.

Wechter neither shows nor suggests that non-alpha tocopherols are effective in treating or ameliorating symptom(s) of neuronal damage associated with a cerebral ischemic condition by reducing neuronal damage. As discussed above, thromboembolic disease in general, and platelet aggregation in particular, are not considered "symptoms of neuronal damage." That is, while thromboembolic disease is one of many possible causes of stroke or cerebral ischemia, it is not a symptom of the neuronal damage (e.g., cell death, cerebral tissue ischemia, cognitive dysfunction) that ensues from cerebral ischemia.

Further, applicants respectfully disagree with the Examiner's assertion that it is general knowledge to persons skilled in the art of neurology that non-alpha tocopherols such as gamma tocopherol have the properties which the Examiner has attributed to them. Even if, for the sake of argument, such properties were considered to be general knowledge of neurologists, the Examiner has provided no reason or motivation to combine such knowledge with the teachings of Wechter. Further, if one were to combine the foregoing teachings along the lines suggested by the Examiner, there is no reason to believe that an anti-oxidant composition would reduce neuronal damage associated with cerebral ischemia. Accordingly, since the Examiner has provided no motivation to combine the teachings cited and has provided no evidence that such combination of teachings would achieve the results of the applicant's claimed invention, such teachings cannot be said to render obvious the applicants' claimed invention.

In view of the foregoing remarks, applicants respectfully submit that the claimed invention is not obvious over the combination of Wechter and teachings cited by the Examiner. Accordingly, withdrawal of this rejection is respectfully requested.

B. Claims 1-57 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Chabrier et al., WO 98/09653 ("Chabrier"). It is the Examiner's position that Chabrier teaches the use of tocopherols to treat cerebral infarction, and therefore, ischemia. The Examiner acknowledges that Chabrier teaches administration of other active principles in addition to tocopherols, but asserts that persons skilled in the art of neurology would have been motivated to administer non-alpha tocopherols [alone] to treat cerebral ischemic conditions in view of Chabrier's disclosure.

1. The Invention. The invention is described in the previous section (A) above.

2. The Cited Prior Art. WO 98/09653 ("Chabrier") is a French document cited by the Examiner. Chabrier teaches the use of trappers of reactive forms of oxygen *in combination with* nitrous oxide (NO) synthase blocking compounds to reduce neuronal damage as a result of cerebral ischemia. Tocopherols are classified by Chabrier as trappers of reactive forms of oxygen (page 6, lines 17-19). Chabrier shows that compounds that are trappers of reactive

forms of oxygen are ineffective in the absence of NO synthase blocking agents. For example, at page 9, lines 23-27, Chabrier reads (in translation): "The association of an inhibitor of the NO synthase and a trapper of reactive forms of oxygen shows a highly significant protective effect on the focal cerebral ischemia *while the effect of the NO synthase inhibitor or the trapper of reactive forms of oxygen taken separately and in the doses used is not significant.*" [emphasis added] Further, in a working example of the rat middle cerebral artery occlusion model of focal cerebral ischemia (page 12) data are presented that show that while the combination of an inhibitor of NO synthase and a trapper of free oxygenated radicals provides protection against neuronal death, neither compound is effective when administered alone (see data table, top of page 13, where group 1 is placebo, group 2 is treated with NO synthase inhibitor alone, group 3 is treated with trapper of free oxygenated radicals alone, and group 4 is treated with the combination of NO synthase inhibitor and trapper of free oxygenated radicals). Only group 4 (combination) shows a significant reduction in neuronal damage, compared to the placebo group. Thus Chabrier teaches that a combination of ingredients, rather than the anti-oxidant alone, is necessary to provide protection against neuronal damage. Consequently, it cannot be said that Chabrier describes or suggests the use of non-alpha tocopherols (or their metabolites) in a method of reducing a symptom of neuronal damage associated with a cerebral ischemic condition, nor does Wechter show or suggest that non-alpha tocopherols or their metabolites are effective to reduce neuronal damage associated with cerebral ischemia.

3. Analysis. The Examiner acknowledges that the applicants' claimed invention differs from Chabrier, because Chabrier includes the administration of other active principles in addition to tocopherols. In fact, as described in paragraph 2, above, Chabrier *teaches away* from the use of tocopherols alone, since by way of description and example, Chabrier shows that tocopherol-like compounds (trappers of free oxygenated radicals) are ineffective against neuronal damage. Consequently, in view of the teaching of Chabrier, persons skilled in the art would not be motivated to administer non-alpha tocopherols in an attempt to reduce neuronal damage associated with cerebral ischemia.

In view of the foregoing remarks, applicants respectfully submit that the claimed invention cannot be said to be obvious over Chabrier. Accordingly, withdrawal of this rejection is respectfully requested.

In view of the foregoing, applicants respectfully request withdrawal of the Examiner's rejections under 35 U.S.C. §103(a).

Summary

Applicants respectfully submit that all issues raised in the Office action have been properly addressed in this response and that the claims pending in the application are now in condition for allowance. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, she is encouraged to contact the undersigned at the telephone number provided below.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is entitled "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 502247** referencing docket no. 0109-UTL.

An associate Power of Attorney was filed in the present case on September 4, 2002, granting the undersigned power to prosecute the present patent application.

Respectfully submitted,

Dated: Nov. 8, 2002

By: _____

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1, 8 and 10 have been amended, as follows:

1. (Amended) A method for treating and/or ameliorating [the] a symptom[s] of neuronal damage associated with a cerebral ischemic condition in a mammalian subject, comprising administering to the subject an effective amount of a non-alpha tocopherol enriched tocopherol composition, and by said administering, reducing neuronal damage related to said cerebral ischemic condition.

8. (Amended) The method of claim 3 wherein said gamma-tocopherol metabolite is 2,7,8-trimethyl-2-(β-carboxy-ethyl)-6-hydroxy chroman (gamma-CEHC).

10. (Amended) The method of claim 9 wherein the occlusion is due to a [thromboembolis] thromboembolus.

New claims 58-63 have been added:

58. (New) The method of claim 1, wherein said neuronal damage is neuronal cell death.

59. (New) The method of claim 1, wherein said neuronal damage is total cerebral infarct volume.

60. (New) The method of claim 1, wherein said neuronal damage is total cerebral ischemic damage.

61. (New) The method of claim 1, wherein said neuronal damage is cerebral tissue edema.

62. (New) The method of claim 1, wherein said neuronal damage is cognitive dysfunction.